The Comparison Impacts of Ginkgo Biloba and Clonazepam on Tinnitus Intensity Improvement in Individuals with Subjective Tinnitus

AMER SALIH KHALAF[1], AMMAR MOHAMMED ALWAN[2]
[1, 2]Assistant professor of otolaryngology, Tikrit medical college, University of Tikrit/Iraq
amer.s@tu.edu.iq
ammar2000@tu.edu.iq

Abstract

Background and aim: Tinnitus is one of the most widespread ear, throat, and nose (ENT) disorders, and it has been treated with a variety of herbal and chemical medications. The comparison impacts of Ginkgo biloba (G. biloba) and Clonazepam in improving subjective tinnitus was the main purpose of this research. Material & methods: 68 patients with subjective tinnitus were selected for this work and classified into 2 identical groups. G. biloba was given to the first group (n = 34), while Clonazepam was given to the second group (n = 34), all participants are given six weeks of treatment. The parameters of adverse quality of life, tinnitus intensity, and treatment response levels were examined before and after treatment to evaluate the effect of these two mentioned drugs on changing these parameters. Results: The outcomes of this work revealed that tinnitus intensity (IT) in patients receiving clonazepam was 6.81±2.16 and 6.23±2.19 before and after treatment, respectively, but this rate for patients receiving G. biloba was 6.72±2.12 and 6.59±2.25, respectively. The results showed that both clonazepam and G. biloba had a significant impact on the variable "adverse quality of life" (P <0.05). The status of tinnitus remained unchanged at only 14.7% of patients receiving clonazepam, whereas this rate was 47.1% in patients receiving G. biloba. Conclusion: It may be stated based on the research findings that G. biloba had little effect on the recovery of tinnitus, while clonazepam was significantly more effective than G. biloba.

Keywords: Tinnitus, Ginkgo biloba, Clonazepam, Ear

1. Introduction

Tinnitus is one of the most widespread ENT disorders with an incidence rate of 14.2% in adults. In 3-5% of people, this disease is considered annoying and a serious problem [1]. According to United States reports, 50 million people suffer from tinnitus [2]. Tinnitus is a disease that can be both subjective and objective. Objective tinnitus is a common disease caused by abnormal nerve activity. The occurrence of objective tinnitus in the community is between 7-20% and at the age of over 48 was 13% [3-6]. Tinnitus is said to increase with age and is more common among women [7, 8]. Tinnitus is a complex and multifactorial cause. Although known causes of tinnitus include stress and anxiety, allergies, loud noise exposure, anti-inflammatory drugs, antibiotics, painkillers, and other medications, however, the fundamental reason for tinnitus in many cases remains unknown.

Tinnitus is sometimes associated with depression, anxiety, restlessness and other mood disorders [9]. These patients often complain of sleep disorders and usually, this disease is annoying for them and disturbs their attention and relaxation [10]. The disease usually resolves spontaneously and no specific treatment for it has been reported to date. Vasodilators by using corticosteroids, anticonvulsants, antispasmodics, lidocaine, benzodiazepines, and others, were used as supportive therapies [7].

Clonazepam, which is an anti-anxiety and anti-seizure drug, is prescribed to prevent seizures. Clonazepam belongs to the benzodiazepine family and therefore has a sedative effect and acts like heroin on the consumer. Clonazepam activates the central nervous system and by acting on gamma-aminobutyric acid, which is one of the neurotransmitters in the brain causes a state of intoxication with relaxation in the consumer [11].

G. biloba (Folium Ginkgo) is a completely dried leaves of the plant (G. biloba) from the Ginkgoaceae genus. Ginkgo leaf contains a wide range of phytochemicals such as lipids, alkanes, sterols, benzenoids, phenylpropanoids, flavonoids, carbohydrates and terpenoids [12, 13]. Hearing loss, dizziness, and tinnitus are all treated clinically with ginkgo extracts. In European countries, this plant is broadly used to cure tinnitus [14]. Due to the widespread publicity for the usage of G. biloba for the management of tinnitus and also because Clonazepam is one of the most widely used drugs for the treatment of this disease [11], so the main target of this work was to assess the effectiveness of Clonazepam and G. biloba in reducing the severity of tinnitus in patients with subjective tinnitus. To our best knowledge, this comparative study is the first to be conducted in this way and therefore this adds to the level of innovation of the present study.

2. Material and Methods

In this study, 68 patients with subjective tinnitus who were referred to an ENT clinic being initially asked for an audiogram to diagnose tinnitus, as well as a complete history was obtained for a definitive diagnosis of subjective tinnitus, then they were examined for organic anatomical and infectious symptoms by a complete ear, head and neck examination. Inclusion criteria for the research comprised: individuals with tinnitus between the ages of 18 and 70 who did not have specific pathological examinations and exclusion criteria included: previous use of G. biloba, use of anticoagulants, history of hypertension, pregnancy or intention to become pregnant, not being in a good

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general condition, observing some unpredictable side effects and patient dissatisfaction.

Upon selection, patients were randomly classified into 2 parts. The first group (n=34) treated with G. biloba and the second group (n=34) received Clonazepam. The patients of these two groups were matched in terms of age and sex. According to the research background, the treatment lasted 6 weeks, and the dose of G. biloba was 160 mg (including 4 tablets of 40 mg) taken twice a day (2 tablets each time), while the dose of Clonazepam was 2 mg (including 4 tablets of 0.5 mg) taken at bedtime [11].

Prior to beginning therapy and following the completion of the course of treatment, patients were evaluated and a questionnaire related to their history was completed. It should be mentioned that the questionnaire used in this study, in addition to measuring individual and clinical variables, other criteria such as visual analogue scale (VAS) and tinnitus severity index (TSI) were measured. The TSI questionnaire is a standard questionnaire whose validity and reliability have been confirmed and it has been used in similar previous studies [15, 16]. The questionnaire consisted of 12 questions, 11 of which were about the effects of tinnitus on attention, sleep and daily activities, and each question, from 1 to 5 points ("never", "rarely", "sometimes", "usually", and "often", respectively for the labels) allocated. Question 12 was also about the response to treatment, which had four options including "unchanged", "slightly improved", "improved" and "completely improved" and for these options, scores of zero, 1, 2, and 3, respectively, were assigned. In this study, the criteria for deciding on the effectiveness of the two drugs were as follows.

The first criterion was the severity of tinnitus or the VAS criterion, in which the patient indicated the height of his/her tinnitus on a numerical graph ranging from zero to 10 (meaning the highest intensity of tinnitus imaginable for a person).

The second criterion for undesirable changes in the patient's quality of life includes feelings of restlessness, fatigue, impaired attention, and impaired social activity, not enjoying life, and impaired sleep quality.

The third criterion was the response to the above-mentioned treatment.

Due to the normality of quantitative variables, the data were collected using SPSS-Ver.21 software and independent sample T-test and paired sample T-test were used at a significant level ($\alpha = 0.05$).

3. Results & Discussion

Based on the outcomes of the research, it was found that the number of patients in the group receiving G. biloba was 19 (55.9%) and 18 (52.9%), respectively, while for patients in the group receiving Clonazepam, this amount was equal to 18 (52.9%), and 16 (47.1%), respectively. The highest percentage of patients in both groups in terms of age is related to the age group of 35-52 years, while in terms of occupation, patients with self-employment were the highest percentage of patients with tinnitus in this study. Furthermore, the results showed that 73.5% of the participants in the Clonazepam group and 67.6% of the participants in the G. biloba group had tinnitus durations of more than 6 months. Most patients who received Clonazepam (70.6%) and G. biloba (73.5%) had tinnitus in their right ear. The majority of patients in both groups had durations of daily tinnitus of about one minute (67.6% of the group receiving G. biloba and 70.6% of the group receiving Clonazepam) (Table 1).

Based on the statements of the patients examined, 47.1% of patients who received Clonazepam and 41.2% of patients who received G. biloba had a long history of loud noise. 52.9% of patients that received Clonazepam and 50.0% of patients that received G. biloba reported that they suffered from hearing loss. Moreover, 55.9% and 52.9% of patients that received Clonazepam and G. biloba, respectively, reported that tinnitus was annoying when silent (Figure 1).

The outcomes of the work indicated that the tinnitus intensity (IT) in the group of patients that received clonazepam, before and after treatment was 6.81±2.16 and 6.23±2.19, respectively, whereas 6.72±2.12 and 6.59±2.25, respectively, were obtained from patients that received G. biloba. Furthermore, based on the results, it was found that the mean amount of IT before treatment was not significantly different between the two groups ($P > 0.05$), while after treatment, a significant difference was observed ($P < 0.05$), as clonazepam group had less IT amount than the G. biloba group (Table 2).

The results showed that both clonazepam and G. biloba had a significant impact on the variable "adverse quality of life", in other words, both drugs were significantly effective in reducing this variable ($P < 0.05$). Moreover, the amount of adverse quality of life, both before and after drug administration was not significantly different between the two groups with each other ($P > 0.05$) (Table 3).

Moreover, in terms of treatment response levels, clonazepam was significantly more effective than G. biloba, as tinnitus status remained unchanged at only 14.7% of patients that received clonazepam, whereas this amount was 47.1% in patients that received G. biloba (Table 4).

Based on the information obtained from the severity of tinnitus in patients before and after treatment in the current research, it can be said that G. biloba is not statistically effective in reducing objective tinnitus compared to clonazepam ($P > 0.05$). Numerous studies have been performed on the therapeutic effect of G. biloba in individuals with tinnitus, most of which contradicts the discoveries of this work, so that some studies have reported the effectiveness of G. biloba in the management of tinnitus [14-18], and some other researches described it as unsuccessful or having a low effect [11-19].

Results of the study of Orhan et al. [19] on 90 persons with a mean age of 52.3 years showed that the symptoms of persons with tinnitus significantly improved after treatment with trimetazidine, betahistine and G. biloba. Also, regarding the comparison of improvement in the three groups receiving the above-mentioned drugs, G. biloba was very effective in improving patients' symptoms compared to the other two drugs Canis et al. [20] showed that G. biloba had very little effect on reducing IT compared to clonazepam throughout a 2-month treatment period in a study of 27 male and 11 female with tinnitus in the age range of 16-80 years [11]. Moreover, Canis et al. [20] found that the impacts of simvastatin and G. biloba on lowering the severity of tinnitus were not significant [21], and the results of these researches are similar to the discoveries of the present study.

YARMOHAMMADI et al. [21] reported that receiving 40 mg of G. biloba twice daily for 2 weeks by patients with tinnitus caused a relative improvement in 53.3% of them [22], and these results did not match the results of the current study. Rejali et al. [22] reported that patients were treated daily with 120 mg of G. biloba for 12 weeks, and the results of this study showed that

treatment with G. biloba was effective in only 21.6% of patients [23]. In the current research, G. biloba was shown to be moderately effective in improving tinnitus in 11.7% of participants. A review study found that G. biloba was much less effective in treating tinnitus. This research informed that the choice of therapies for individuals has been helpful not just in terms of lowering costs, but also in terms of preventing patients from seeking and choosing other unsuccessful therapies [24]. Researches indicated that G. biloba, a monoamine-oxidase inhibitor, due to the presence of flavonoids, myristin, and quercetin and the group of ginkgolide and bilobalide terpenoids, can be effective in improving patients with tinnitus due to ischemia [25]. But this effect may not be as effective as other tinnitus medications such as clonazepam.

Table 1: The demographic characteristics of the studied patients in this study based on treatment type

Variables		Number (%)	
		Treatment with Clonazepam	Treatment with G.biloba
Sex	Male	18 (52.9)	19 (55.9)
	Female	16 (47.1)	15 (44.1)
Age (year)	18-35	6 (17.6)	7 (20.6)
	35-52	17 (50)	18 (52.9)
	52-70	11 (32.4)	9 (26.5)
Job	Self-employment	13 (38.2)	14 (41.2)
	Employee	10 (29.4)	6 (17.6)
	Housewife	9 (26.5)	11 (32.4)
	Unemployed	2 (5.9)	3 (8.8)
Tinnitus duration	6 months≥	9 (26.5)	11 (32.4)
	6 months<	25 (73.5)	23(67.6)
Ears involved with "tinnitus"	Left	10 (29.4)	9 (26.5)
	Right	24 (70.6)	25 (73.5)
Duration of daily tinnitus	About an hour	10 (29.4)	11 (32.4)
	About a minute	24 (70.6)	23(67.6)

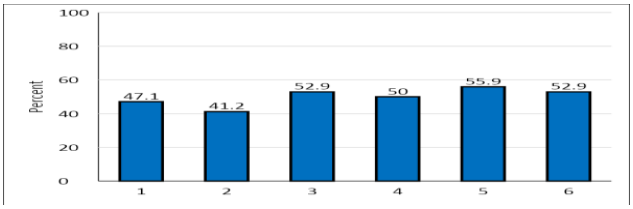

Figure 1. The long history with a loud voice, having hearing loss and annoying tinnitus in patient's groups receiving drugs Clonazepam and G.biloba

Table 2: The comparison of the tinnitus intensity before and after intervention in the two groups

Groups	Tinnitus intensity		P (significant level)
	Before intervention (Mean ± S.D)	After intervention (Mean ± S.D)	
Receiving of clonazepam	6.81±2.16	6.23±2.19	0.002
Receiving of G.biloba	6.72±2.12	6.59±2.25	0.231
Independent Sample T-test (significant level)	0.851	0.049	-

Table 3: The comparison of the adverse quality of life before and after intervention in the two groups

Groups	Adverse quality of life		P (significant level)
	Before intervention (Mean ± S.D)	After intervention (Mean ± S.D)	
Receiving of clonazepam	34.85±9.79	30.32±9.15	0.003
Receiving of G.biloba	33.59±8.52	31.43±7.64	0.009
Independent Sample T-test (significant level)	0.283	0.301	-

Table 4: The comparison of the treatment response levels in the two groups

Groups	Treatment response levels			P (significant level)
	Unchanged [N (%)]	Slightly improved [N (%)]	Moderately improved [N (%)]	
Receiving of clonazepam	5 (14.7)	12 (35.3)	17 (50)	0.005
Receiving of G.biloba	16 (47.1)	14 (41.2)	4 (11.7)	

4. Conclusion

It can be stated based on the research findings that although G. biloba has had little effect on the improvement of tinnitus, but it is less effective than clonazepam and cannot be used as a reassuring drug to treat tinnitus. Clonazepam, on the other hand, was significantly more effective than G. biloba. Therefore, it is recommended to use other effective drugs in this field or other non-pharmacological treatments for faster and more efficient recovery of patients with tinnitus.

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